

Epidemiology and Prevention of Carbapenem-Resistant Enterobacteriaceae

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The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

National Center for Emerging and Zoonotic Infectious Diseases
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Objectives

- ❑ Describe the epidemiology of carbapenem-resistant Enterobacteriaceae (CRE) in the United States
- ❑ Review measures necessary to halt transmission
- ❑ Recognize the importance of a regional approach to CRE control

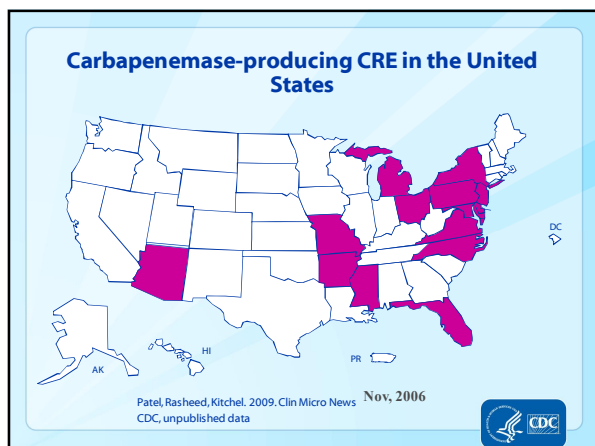
Enterobacteriaceae

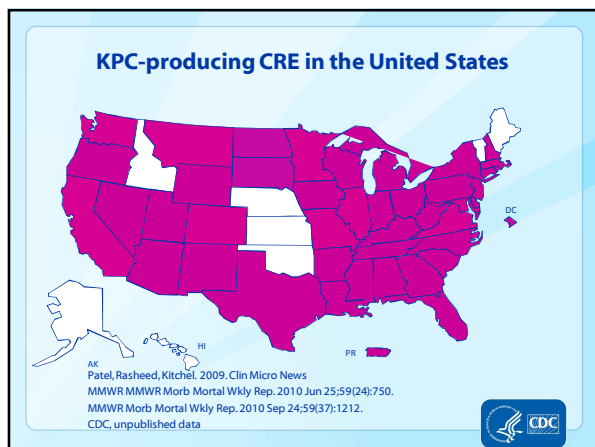
- ❑ Normal human gut flora & environmental organisms
- ❑ More than 70 species
- ❑ Range of human infections: UTI, wound infections, pneumonia, bacteremia
- ❑ Important cause of healthcare- and community-associated infections
 - Some of the most common organisms encountered in clinical laboratories

Pathogens Reported to NHSN 2009-2010					
	Overall percentage	CLABSI	CAUTI	VAP	SSI
<p>These three groups of organisms make up about 25% of organisms reported to NHSN Device and Procedure module</p>					
<i>P. aeruginosa</i>	8% (5)	4%	11%	17%	6%
<i>Enterobacter</i> spp.	5% (8)	5%	4%	9%	4%
Sievvert D, et al. Infect Control Hosp Epidemiol 2013; 34: 1-14					

Enterobacteriaceae	
<ul style="list-style-type: none"> Resistance to β-lactams has been a concern for decades <ul style="list-style-type: none"> β-lactamases Extended-spectrum β-lactamases Carbapenems <ul style="list-style-type: none"> Imipenem, meropenem, doripenem, ertapenem Resistance before 2000, combination of mechanisms <ul style="list-style-type: none"> 1986-1990 in NNIS 2.3% of <i>Enterobacter</i> NS to imipenem 	

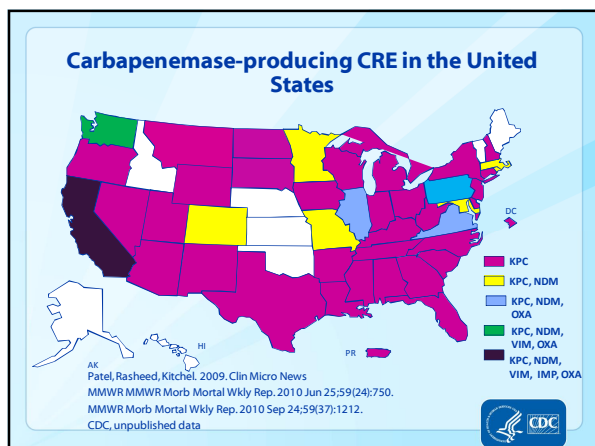
<p>ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151-1161 0066-4804/01/\$10.00+0 DOI: 10.1128/AAC.45.4.1151-1161.2001 Copyright © 2001, American Society for Microbiology. All Rights Reserved.</p> <p>Vol. 45, No. 4</p> <p>Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of <i>Klebsiella pneumoniae</i> HESNA YIGIT,¹ ANNE MARIE QUEENAN,² GREGORY J. ANDERSON,¹ ANTONIO DOMENECCH-SANCHEZ,³ JAMES W. BIDDLE,⁴ CHRISTINE D. STEWARD,¹ SEBASTIAN ALBERTI,⁴ KAREN BUSH,² AND FRED C. TENOVER^{1*}</p> <p>* Isolate collected in 1996 during an ICU surveillance project from NC * Class A β-lactamase</p>	
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Carbapenemases

Enzyme	Classification	Activity
KPC	Class A	Hydrolyzes all β -lactam agents
NDM-1	Class B: metallo- β -lactamase (MBL)	Hydrolyzes all β -lactam agents except aztreonam
IMP		
VIM		
OXA	Class D	Hydrolyzes carbapenems but not active against 3 rd generation cephalosporins



Change in CRE incidence, 2001-2011

Organism	National Nosocomial Infection Surveillance system, Number (%) of isolates			National Healthcare Safety Network, Number (%) of isolates		
	2001 Isolates	2001 Tested	2001 Non-susceptible	2011 Isolates	2011 Tested	2011 Non-susceptible
<i>Klebsiella pneumoniae</i> and <i>oxytoca</i>	654	253 (38.7)	4 (1.6)	1,902	1,312 (70.0)	136 (10.4)
<i>E. coli</i>	1,424	421 (29.6)	4 (1.0)	3,626	2,348 (64.8)	24 (1.0)
<i>Enterobacter aerogenes</i> and <i>cloacae</i>	553	288 (52.1)	4 (1.4)	1,045	728 (69.7)	26 (3.6)
Total	2,631	962 (36.6)	12 (1.2)	6,573	4,388 (66.8)	186 (4.2)

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Active CRE surveillance

■ MuGSI (Multi-site Gram-Negative Surveillance Initiative) project

- Active, laboratory-initiated, population-based surveillance for CRE and CR *Acinetobacter* (CRAB) in 6 US sites (sterile sites and urine)
- Pilot 8/11 to 12/11 (3 sites)
 - ~ 72 CRE (64 patients) - most (59) from one site (OR had 3)
 - ~ Urine most common source (89%)
 - ~ CR *K. pneumoniae* most common (68%)
 - ~ Most with onset outside hospital (66%)
 - o 41/47 (87%) had healthcare exposures (72% hospitalization)
 - o 6 were community onset without healthcare exposures

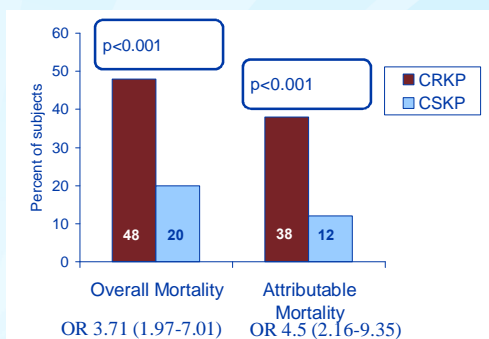
Kallen et al. ID Week 2012, San Diego

Why are CRE Clinically and Epidemiologically Important?

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- Cause infections associated with high mortality rates

Mortality



Patel et al. Infect Control Hosp Epidemiol 2008;29:1099-1106

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- ❑ Cause infections associated with high mortality rates
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- ❑ Treatment options are limited
 - Pan-resistant strains identified
 - Could be decades before new agents are available to treat

Pan-Resistant Enterobacteriaceae

- ❑ Report from New York City of 2 "Panresistant" *K. pneumoniae*
 - 1 patient died
 - 1 had continuing asymptomatic bacteremia

Table 1. Antimicrobial susceptibility patterns for *Klebsiella pneumoniae* isolates.

	MIC value, µg/mL	
	Patient 1: urine specimen	Patient 2: blood specimen
Aminoglycoside		
Amikacin	>64	>64
Amoxicillin	>32	>32
Aztreonam	>64	>64
Cefazolin	>64	>64
Cefepime	32	>16
Ceftazidime	>64	>64
Ciprofloxacin	>4	>4
Gentamicin	>16	>16
Piperacillin/tazobactam	>128	>128
Tobramycin	>16	>16
Trimethoprim-sulfamethoxazole	>256	>256
Meropenem	256	NA
Ertapenem	>16	>16
Imipenem	>16	>16
Moxifloxacin	NA	>4
Tigecycline	>8	>8
Polymyxin B ^a	8	>16

NOTE: All susceptibility testing, except for polymyxin B, was done using the Vitek 2 automated system (Becton Dickinson). MIC, minimum inhibitory concentration; NA, not available.
^a Antimicrobial agents indicated with "16" instead of an MIC value were read as susceptible by the automated system, but findings were confirmed on the basis of disk diffusion (disk reaction testing results indicating the presence of *K. pneumoniae* catapoximase activity).

^b Tested using E-test.

Elemam A, et al. Clin Infect Dis 2009; 49:271-4

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- ❑ Potential for spread into the community
 - *E. coli* common cause of community infection

MDR GNRs in the Community

❑ ESBLs

- 40 patients with CTX-M *E. coli* from urine in a facility in Texas
 - ~ 30/40 were isolated from outpatients, 7 (18%) had no documented contact with the healthcare system in previous 6 months and no comorbidities
- Swedish travelers – 100 travelers outside of Northern Europe
 - ~ 24 came back with ESBL in stool (mostly NDM)
 - ~ 7/8 to India, 10/31 to Asia
 - ~ Development of gastroenteritis a risk factor
 - ~ 5/21 persistently colonized

Lewis JS, et al. Poster Presentation, 49th ICAAC 2009, San Francisco
Tangden T et al. AAC 2010: 3564-3568

MDR GNRs in the Community

❑ NDM

- Identified in *K. pneumoniae* in river in Hanoi, Viet Nam
- Cause of community-onset infections in India
 - ~ In one survey, isolates from 2 sites often from community acquired UTIs
- Gene for NDM detected in 2/50 drinking water samples and 51/171 water seepage samples from New Delhi

Isozumi R et al. EID 2012: 1383-4
Kumarasamy K Lancet ID 2010;
Walsh TR Lancet ID 2011:355-362

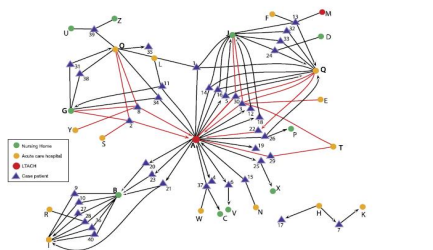
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- ❑ Potential for spread into the community
 - *E. coli* common cause of community infection
- ❑ In most areas in the United States this organism appears to infrequently identified

Facilities Reporting at least One CRE (CAUTI or CLABSI) to NHSN, First Half of 2012

Facility characteristic	Number of facilities with CRE from a CAUTI or CLABSI (2012)	Total facilities performing CAUTI or CLABSI surveillance (2012)	(%)
All acute care hospitals	181	3,918	(4.6)
Short-stay acute hospital	145	3,716	(3.9)
Long-term acute care hospital	36	202	(17.8)

ROLE OF LONG-TERM CARE



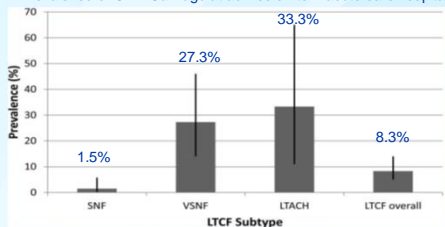
KPC outbreak in Chicago, 2008

- " Of 40 KPC patients, only 4 definitively acquired KPC in acute care hospital
- " Most (60%) linked to 1 LTACH

Won et al. Clin Infect Dis 2011; 53:532-540

CRE Prevalence in LTCF: By Type

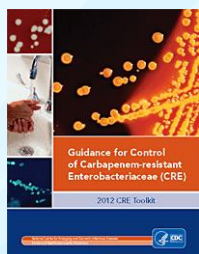
Prevalence of CRE Carriage at admission to 4 acute care hospitals



0% from those admitted to the community

Prabaker K et al. ICHE 2012; 33:1193-1199

Prevention



<http://www.cdc.gov/hai/organisms/cre/cre-toolkit/>

Surveillance and Definitions

- ❑ **Facilities/Regions should have an awareness of the prevalence of CRE in their Facility/Region**
 - Could concentrate on *Klebsiella* and *E. coli*
 - Could concentrate on those NS to a carbapenem OR add R to a third-generation cephalosporin to the definition to increase specificity for KPC
 - ~ Ceftiaxone, cefotaxime, ceftazidime
- ❑ **No easy way right now to check for carbapenemases**

Interventions

Core

- Hand hygiene
- Contact Precautions*
- HCP education
- Minimizing device use
- Patient and Staff cohorting
- Laboratory notification*
- Antimicrobial stewardship
- CRE Screening*

Supplemental

- Active surveillance cultures
- Chlorhexidine bathing

* Included in 2009 document

Contact Precautions

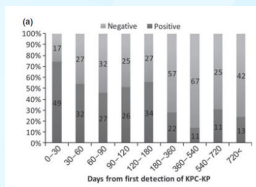
- ❑ CP for patients colonized or infected with CRE
- ❑ Systems in place to identify patients at readmission
- ❑ Education of HCP about use and rationale behind CP
- ❑ Adherence monitoring
- ❑ Consideration of pre-emptive CP in patients transferred from high-risk settings

Contact Precautions in Long-Term Care

❑ CP could be modified in these settings:

- CP should be used for residents with CRE who are at higher risk for transmission
 - ~ Dependent upon HCP for their activities of daily living
 - ~ Ventilator-dependent
 - ~ Incontinent of stool
 - ~ Wounds with drainage that is difficult to control
- For other residents the requirement for Contact Precautions might be relaxed
- Standard Precautions should still be observed

Duration of KPC Carriage

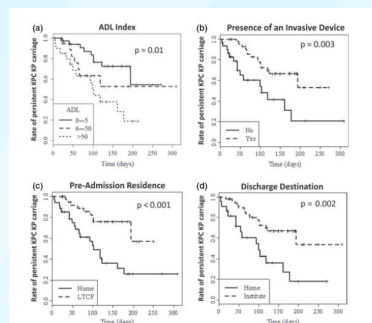


~ KPC Patients swabbed 5 to 6 times (at discharge, 2 weeks, 1, 2, 3 mos post-discharge)

~ Overall resolution of carriage (2 consecutive negatives)
62/125 (52%)
~ 39% of recently identified patient
~ 79% of remotely identified patients (> 4 mos prior)

Feldman et al. Clin Micro and Infect 2012;19:E190-196

Risk Factors for Persistent Carriage



Feldman et al. Clin Micro and Infect 2012;19:E190-196

Risk Factors for CRE at Readmission

Case-control study of 66 patients with CRE

- Compared those positive at readmission with those that were negative

TABLE 2. Distribution of the Total Number of Predictors among Carbapenem-Resistant Enterobacteriaceae (CRE) Screen-Positive Case Patients and CRE Screen-Negative Control Patients and the Probability of Having a Positive Screen Test on the Basis of the Total Number of Predictors

No. of predictors	Positive screen test (n = 23)	Negative screen test (n = 43)	Probability of a positive screen test, % (95% CI)
0	4	24	14.3 (4.9-32.7)
More than 1	19	19	50.0 (33.3-66.7)

NOTE. Predictors included prior fluoroquinolone use (during the 30 days preceding the survey), transfer from an institution or another hospital, and time interval less than or equal to 3 months since the first CRE test. CI, confidence interval.

Schechner V et al. ICHE 2011;32:497-503

Number of Screens to Determine CRE Clearance

- “ One negative (N=97) – 65 (67%) cleared
- “ Two negative (N=67) – 57 (85%) cleared
- “ Three negative (N=50) – 45 (90%) cleared

TABLE 2. Validity of different criteria for defining clearance of KPC KP carriage

Criteria*	Study group	Total number of patients, n	Patients with negative tests, n	Patients with KPC KP clearance, n (%)
1	REC ^b	69	54	29 (54)
	REM ^c	49	43	36 (84)
2	REC ^b	55	31	25 (81)
	REM ^c	42	34	31 (89)
3	REC ^b	52	19	16 (84)
	REM ^c	39	31	29 (94)

*Criteria, number of consecutive negative tests (without subsequent positive test) necessary for defining clearance of KPC KP carriage.

^bKPC KP, KPC-producing *Escherichia coli* pneumonia.

^c%, ratio of the number of patients with KPC KP clearance to the number of patients with negative tests.

^dREC, rectus (1-4 months) KPC KP acquisition group.

^eREM, rectus (1-4 months) KPC KP acquisition group.

Feldman et al. Clin Micro and Infect 2012;19:E190-196

Patient and Staff Cohorting

- ❑ CRE patients in single rooms (when available)
- ❑ Cohorting (even when in single rooms)
- ❑ Staff cohorting
- ❑ Preference for single rooms should be given to patients at highest risk for transmission such as patients with incontinence, medical devices, or wounds with uncontrolled drainage

CRE Screening

- ❑ Studies suggest that only a minority of patients colonized with CRE will have positive clinical cultures
 - CRKP Point prevalence study in Israel (5.4% prevalence rate); 5/16 had a positive clinical culture for CRKP.
 - A study of surveillance cultures at a US hospital found that they identified a third of all positive CRKP patients. Not having these patients in CP resulted in about 1400 days of unprotected exposure.

Weiner-Well et al. J Hosp Infect 2010;74:344-9

Calfee et al. ICHE 2008;29:966-8

CRE Screening

- ❑ Used to identify unrecognized CRE colonization among contacts of CRE patients
- ❑ Stool, rectal, peri-rectal
- ❑ Link to laboratory protocol
http://www.cdc.gov/ncidod/dhqp/pdf/ar/Klebsiella_or_E.coli.pdf
- ❑ Applicable to both acute and long-term care settings
- ❑ Description of types
 - Screening of epidemiologically linked patients
 - Roommates
 - Patients who shared primary HCP
 - Point prevalence survey
 - Rapid assessment of CRE Prevalence on particular wards/units
 - Might be useful if lab review identifies one or more previously unrecognized CRE patient on a particular unit

Active Surveillance Cultures

- ❑ Screening patients (generally at admission) for CRE
- ❑ Controversial
- ❑ Potential considerations:
 - Focus on patients admitted to certain high-risk settings (e.g., ICU) or specific populations (e.g., from LTCF/LTAC)
 - Patients hospitalized outside the US

Chlorhexidine Bathing

- ❑ Limited evidence for CRE
 - Used effectively in outbreak in LTAC as part of a package of interventions
 - Applied to all patients regardless of CRE colonization status
 - Has shown decrease transmission of MRSA and VRE
- ❑ Some studies suggest CHG bathing may not be done "well"

Munoz-Price et al. ICHE 2010;31:341-7

REGIONAL APPROACH TO CRE PREVENTION

Inter-Facility Transmission of MDROs (Including CRE)

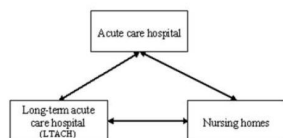


Figure 3. Patient flow among regional health care facilities. Outbreaks of infection with multidrug-resistant organisms have been found to follow the flow of colonized patients across institutions.

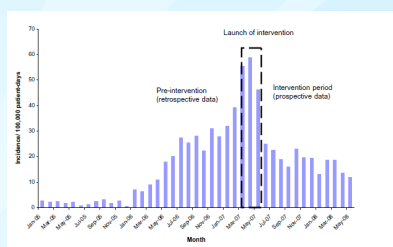
Munoz-Price SL. Clin Infect Dis 2009;49:438-43

Israel Experience

- ❑ KPCs likely originally from US identified in Israel beginning in late 2005
- ❑ By early 2006, increase in cases
- ❑ Initiated National effort to control CRE
 - Mandatory reporting of patients with CRE
 - Mandatory isolation (CP) of CRE patients
 - Staff and patient cohorting
 - Task Force developed with authority to collect data and intervene



79% decrease from highest and last month



Schwaber et al. CID 2011; 848-855

Summary

- ❑ **Carbapenem-resistance among Enterobacteriaceae appears to be increasing**
 - Appears to be driven primarily by the emergence of carbapenemases
- ❑ **Heterogeneously distributed within and across regions**
- ❑ **Has the potential to spread widely**
 - Healthcare and community settings
- ❑ **Most areas in a position to act to slow emergence**
- ❑ **A regional approach to MDRO prevention is required**
 - Public health well-positioned to facilitate and support regional prevention efforts



Thanks for your attention.
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